STUDIES IN THE TREATMENT OF MALARIA—XXXII

SUMMARY OF STUDIES I—XXXI

BY

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The results recorded in the present paper constitute a summary of work on the treatment of malaria carried out at the Liverpool School of Tropical Medicine in the years 1917–1919.

Before considering the various treatments employed, it will be necessary to define certain terms and it will be convenient also to consider certain facts which emerged as the work progressed.

Part I

MALARIA

Only those cases were treated in which parasites were present in the blood at the commencement of treatment. The patient's temperature may, or may not, have been above normal.

RELAPSE

A *parasitic* relapse, febrile or afebrile, i.e., parasites have reappeared in the blood after a negative period induced by treatment.

FEBRILE ATTACKS

A rise of temperature above 100°F., unaccompanied by parasites in the blood within 2–3 days, of which the nature is unknown.

OBSERVATION PERIOD

If we desire to know whether a treatment has cured a patient, i.e., eliminated parasites from his system, it is obvious that the patient must be kept under observation after the treatment. The longer the patient

is kept under observation—by this we mean, not solely clinical observation, but primarily (daily) microscopic examinations of the blood for parasites, the more reasonable will it be to conclude, if the examinations are negative—that he is cured.

The period of observation employed by us was one of 60 days, implying, as we have just said, daily blood examinations. It should be unnecessary to add that *no treatment* was given during the observation period.

FALLACIOUS FIGURES

It is necessary to point out some sources of fallacy in regard to the results of treatment, many examples of which can be found in the literature.

1. *Absence of a microscopic diagnosis of parasites in patients before commencing treatment.* Such cases may be malaria or they may not.
2. *Administration of quinine during the so-called 'observation period'.* The figures relating to relapses are obviously worthless.
3. *Comparison of treatments with different observation periods.*

If the value of two treatments are to be compared, the cases under each treatment must be observed for the *same length of time*, after the cessation of treatment, otherwise the figures for relapses are not comparable, and it is impossible to say which is the better treatment, as in the following example.

Table I.

Treatment	Number of cases treated	Number of cases which relapsed	Number of cases not relapsing but lost sight of before the expiration of 60 days	Number of cases not relapsing in an observation period of 60 days	Relapses	
					Actually observed	Possible maximum
I	100	10	80	10	10%	90%
II	100	30	30	40	30%	60%
III	100	50	0	50	50%	—

4. *Composite figures obtained by summarising the results of various treatments.*

The following is an example :—

Suppose two treatments employed, A and B, and that in the A treatment the relapses were 100 per cent. and that in the B treatment they were 0 ; and further, suppose that 750 cases were under treatment A, 250 under treatment B, then we get the following result :—

	Cases treated	Relapses	Percentage
Treatment A	750	750	100
Treatment B	250	0	0
	1000	750	75

It is correct to say that, of 1,000 cases treated, 75 per cent. relapsed.

Let us repeat the treatments and suppose that the distribution of cases treated now happens to be as follows :—

	Cases treated	Relapses	Percentage
Treatment A	250	250	100
Treatment B	750	0	0
	1000	250	25

It is also correct to say that, of 1,000 cases treated, 25 per cent. only relapsed ; but the figures 25 and 75 have no *real significance.* All that is important that the figures show, is that one treatment was very good, the other very bad.

GRAPH 1.

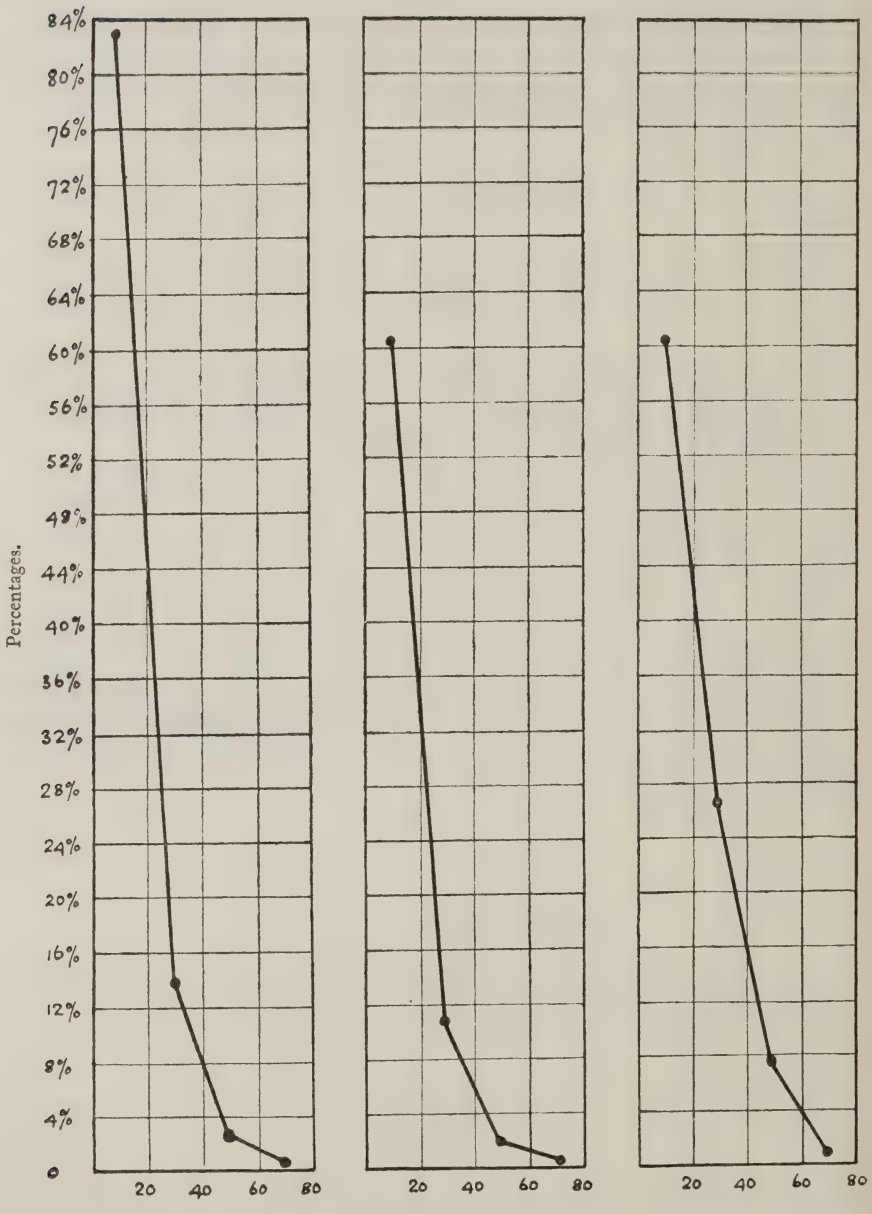
Percentage of total relapses in each 20-day period.

GRAPH 2.

Percentage of cases treated which relapse in each 20-day period.

GRAPH 3.

Percentage of cases treated not having previously relapsed which do so in each 20-day period.



Days after cessation of treatment.

THE TIME AT WHICH RELAPSES OCCUR AFTER CESSATION OF TREATMENT IN SIMPLE TERTIAN MALARIA

The time incidence of relapses can be considered in three ways :—

1. In reference to the *relapses themselves*, i.e., the percentage of the total relapses which occur during each period of time. From an analysis of the time of occurrence of 582 relapses, we found that about four-fifths occur in the first 20 days after treatment, that the majority of the remaining one-fifth occurs in the second 20-day period, i.e., the ratio of the number of relapses in the two periods is about 4 : 1.

2. In reference to the *total cases treated*, i.e., the percentage of cases treated which relapse during each 20-day period of time. Of the cases treated (800), about three-fifths relapse in the first 20-day period, about one-tenth in the second 20-day period : still fewer at later periods, i.e., the ratio of the percentages for the two periods is 6 : 1.

3. In reference to *remainders*, i.e., the incidence among the cases treated less those who have previously relapsed. Of the cases treated (800), about three-fifths relapse in the first 20 days and about one-fourth of ' the remainder ' cases in the second 20-day period. The ratios are here 12 : 5 or 2.4 : 1.

It is possible that, if a large number of cases that had not relapsed in 60 days had been observed for much longer periods, that the values we have given for the first and second 20-day periods would have to be somewhat reduced, but until the actual observations are made, this is purely conjectural.

It must be added that, unless a sufficiently large number of cases are considered, it is not likely that the ratios given above will be observed.

TIME OF ONSET OF THE PAROXYSMS IN SIMPLE TERTIAN MALARIA

From an analysis of 1,000 ' rigors ' or paroxysms, we found that :—

(*a*) Over 90 per cent. of the paroxysms occur during the hours of bodily activity, in our series of cases from 7 a.m. to 6.59 p.m.

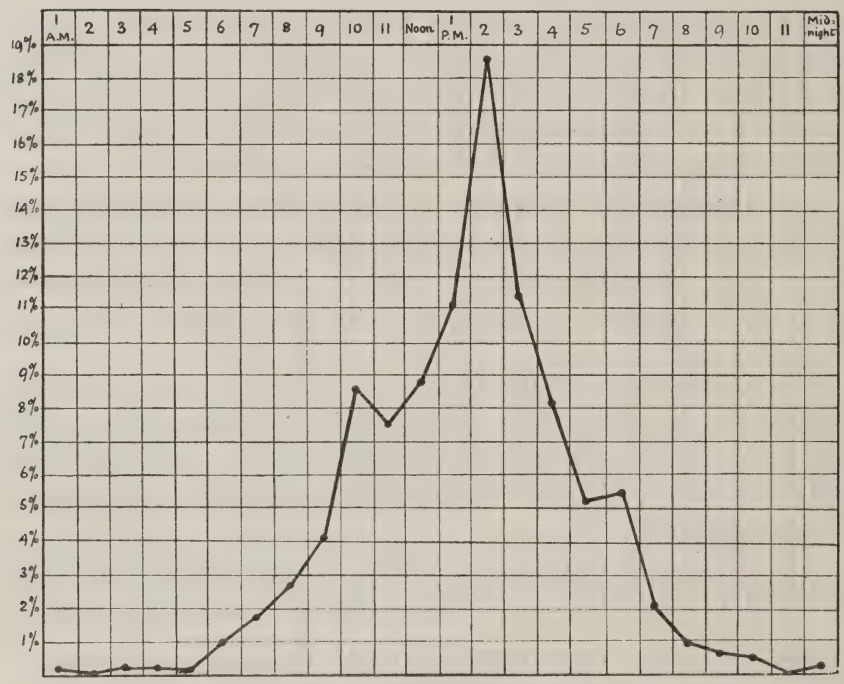
(*b*) The maximum number of paroxysms, about 20 per cent., occurs at 2 p.m.

THE EFFECT OF SEASON ON TREATMENT OF MALARIA

Two series of cases consisting of 76 and 89 patients, respectively, were treated by us at different times of the year with the same treatment, viz., quinine sulphate, grains 90, on two consecutive days only.

In one series the number of relapses was about 40 per cent., in the other, over 90 per cent.

The only factor that we could discover that might account for this difference was that the cases were treated at different times of the year, the good result was obtained in the summer and autumn, the bad result in the winter and spring months.



GRAPH.—Showing the time incidence of 1,000 simple tertian malaria paroxysms; 'Summer' time in operation.

THE MAXIMUM DOSE OF QUININE THAT CAN BE TOLERATED

Quinine sulphate, orally in doses of grains 120 on each of two consecutive days, represents the maximum amount of the drug which can be tolerated by the average case, as the treatment had to be abandoned owing to severe symptoms in five of fifteen cases.

Part II.

TREATMENT OF AN ATTACK

Quinine

(*a*) *Orally.*

Ten grains of quinine sulphate in solution on each of two consecutive days suffice to cut short an attack of simple tertian malaria, and to cause the temporary disappearance of parasites from the cutaneous blood.

While this is so, our routine procedure is to give grains 15, two to three times a day for a few days until the same result is accomplished. The subsequent treatment will be considered later.

(*b*) *Intramuscularly.*

1. *Quinine bihydrochloride.*

Fifteen grains of quinine bihydrochloride in 2 c.c. of water on each of two consecutive days likewise cause the cessation of febrile paroxysms and effect the temporary disappearance of all stages of the parasites from the cutaneous blood. This holds good for *P. vivax* and *P. falciparum.*

2. *Quinine alkaloid.*

Grains 15 to 30 in 1 c.c of sesame oil on each of two consecutive days, has the same effect in cases of simple tertian malaria.

Where the patient can take quinine by the mouth there is usually no necessity for intramuscular injections, but where oral quinine is ineffective, intramuscular quinine remains as a most effective treatment.

(*c*) *Intravenously.*

Quinine bihydrochloride in doses of 10–15 grains in a 10 per cent. solution in normal saline, in one or a series of six injections, causes the cessation of febrile paroxysms and a disappearance of parasites from the cutaneous blood in simple tertian malaria.

In *malignant tertian* malaria these doses do not cause the disappearance of parasites—trophozoites or gametes—from the cutaneous blood.

Arsenic

(*a*) *Organic. Arsenobillon.*

A single intravenous injection, 0.9 gramme, controls the fever, causes the disappearance of *P. vivax* from the cutaneous blood within 24 hours. The same dose has no appreciable effect on the temperature or the parasites in the case of *P. falciparum* or *P. malariæ.*

(*b*) *Inorganic. Liquor arsenicalis.*

In doses of ♏15 daily, failed to control the fever or to cause the disappearance of parasites. In doses of ♏30 daily, the temperature fell to normal within ten days and in 13 of 14 cases parasites disappeared in two to six days.

Silver Arsenic and Antimony

Luargol.

A single intravenous injection of 0.2 gramme, controls the symptoms and causes the disappearance of the parasites in simple tertian malaria.

Antimony

Tartar Emetic.

Intravenous injections of tartar emetic, 2 per cent. solution in one or more doses of 5–15 centigrams, do not control either the rigors or the fever of acute malaria, nor do they cause the disappearance from the blood of any stage of the malaria parasites, whether of *P. vivax* or *P. falciparum.*

Manganese

Collosol manganese 1 c.c. on each of two consecutive days proved to be valueless.

Quitenine and Quinotoxin

The hydrochlorides of these derivatives of quinine proved of no value in the doses used, viz., of about the same amount as that of quinine sulphate which proved effective.

Amylopsin and Trypsin

'Injectio amylopsini' and 'Injectio trypsini' proved to be of no value in the treatment of simple tertian malaria.

Part III.

SUBSEQUENT TREATMENT

We have seen that the immediate effect of quinine and other drugs is to allay the febrile symptoms and to cause the disappearance of parasites, but this condition of apparent cure was, sooner or later, followed by a relapse in the majority of cases. Two questions consequently arose :—

1. The first was, could the condition of apparent cure be *maintained* by continuing the quinine treatment, and if so, how should it be given ?

2. The second was, were these cases in which the administration of quinine was continued for more or less long periods, and which showed no symptoms while taking quinine, really cured ? Would they relapse or not, when treatment was stopped, just as they had done when the treatment had lasted only a few days, or would the number of relapses be now smaller

Question I.

The aspect of the problem that mainly occupied us was, whether if a certain total dose of quinine were given weekly, e.g., grains 30, 60, 90, it were better to administer the quantity on 6 days giving 5, 10, or 15 grains daily, or on two consecutive days only each week, giving 15, 30, or 45 grains daily.

This question was put to the test for a period of eight weeks in a series of cases for each total weekly dose of 30, 60, and 90 grains of quinine sulphate.

An accurate record was kept of the febrile relapses (non-parasitic) and of the parasitic relapses (febrile and afebrile), as determined by the temperature chart and daily blood examinations during the whole of the period.

In each series the record was in favour of the weekly administration of quinine in preference to the daily.

Thus, 30 grains is better administered in the form of two doses of 15 grains, than in the form of six doses of 5 grains.

The best result was obtained by the administration of grains 45 (three doses of grains 15), on each of two consecutive days weekly, this as above stated, giving a better result than grains 15 daily for six days.

An interrupted treatment of 30 grains on each of two consecutive days weekly, also suffices to keep the blood free from trophozoites and to prevent relapses in the majority of cases (while the treatment lasts).

In other words, in order to maintain a patient in a condition of freedom from relapses, an *interrupted* course of quinine is preferable to a *continuous* one.

So far as the actual result was concerned, an equally good one, or nearly so, was obtained in a different way, viz., by giving 15 grains of bihydrochloride intramuscularly on each of the first two days of treatment, and then Liquor arsenicalis ♏30 daily, with two periods of intermission for eight weeks (two weeks on, one week off, two weeks on, one week off, two weeks on).

The comparative figures for this and the previous interrupted quinine treatment are the following :—

	Quinine injections, two only, followed by Liq. arsenicalis ♏30 daily	Quinine sulphate Gr. 45 on two consecutive days weekly for 8 weeks
Percentage of parasitic febrile relapse cases per cases treated (average per week)	2·7	1·8
Percentage of all febrile (parasitic and non-parasitic) cases per cases treated (average per week	8·7	10·3
Number of cases treated...	33	74

What we have just considered is a method of maintaining freedom from relapses *while the treatment is in force.* We shall now consider a different question, viz. :—

Question 2.

This question resolves itself into an enquiry as to whether by any course of treatment, short or long, a curative effect would be obtained, i.e., freedom from relapses after cessation of treatment, over an observation period of sixty days (or longer).

Many methods were tried, but in nearly all, when treatment was stopped, the number of relapses was large, and there is at present no method known which will cure all cases, even if the treatment lasts eight weeks.

Many methods of cure continue however, to be advocated, but they are not supported by trustworthy evidence, more especially in regard to an adequate observation period.

The following two treatments gave us the best results :—

	Number of cases treated	Number of cases not relapsing but lost sight of before the expiration of 60 days	Number of cases relapsing in an observation period of 60 days	Relapses per cent. min.	Relapses per cent. max.	Time of Year.
Liquor arsenicalis minims 30 daily with 1 or 2 periods of intermission with an injection of quinine bihydrochloride on each of the first two days only	32	—	4	12·5	12·5	End of treatment August :—1 case ; September :—17 cases ; October :—14 cases NOTE.—One additional case was not controlled by the treatment.
Novarsenobillon 0·9 grm. intravenously on the 1st, 8th, and 15th days with quinine bihydrochloride grs. 15 intramuscularly on the 1st and 2nd, 8th and 9th, and 16th days.	12	1	—	8·3	16·6	End of treatment December :—12 cases

It is worthy of note that a treatment which is ' good ' whilst it lasts is not necessarily followed by a ' good ' result when it has ceased. Thus the treatment noted above, viz., grains 45 × 2 weekly for eight weeks, while ' excellent ' while it lasted, was followed by 80 per cent. of relapses when the treatment had finished.

Whereas the arsenic treatment also a good one while it lasted, was followed by a ' good ' result also when it had ceased.

THE DISAPPEARANCE OF MALIGNANT TERTIAN GAMETES (CRESCENTS) UNDER QUININE TREATMENT

1. With a dose of grains 30 or 45 daily, crescents do not persist in the blood in the majority of cases for more than three weeks. Whether they would disappear equally rapidly without quinine we did not determine.

2. Similarly with quinine sulphate grains 30 on each of two consecutive days weekly for five weeks, the crescents diminished from 50 per cent. in the first week to 6 per cent. in the fifth week of treatment.

APPENDIX

The Titles, number of volume and date of Publication of the Studies in the Treatment of Malaria (I–XXXI) are given below :—

Annals of Tropical Medicine and Parasitology.

I Intravenous Injections of Tartar Emetic. Vol. XI, p. 91. 1917.

II Intramuscular Injections of Quinine Bihydrochloride in Simple Tertian Malaria. Vol. XI, p. 113. 1917.

III Intravenous Injections of Quinine Bihydrochloride. Vol. XI, p. 149. 1917.

IV Intramuscular Injections of Anylopsin and Trypsin in Simple Tertian Malaria. Vol. XI, p. 165. 1917.

V Intramuscular Injections of Quinine Alkaloid in Simple Tertian Malaria. Vol. XI, p. 173. 1917.

VI Oral Administration of Quinine for Two Consecutive Days only in Simple Tertian Malaria. Vol. XI, p. 283. 1918.

VII Oral Administration of Quinine Sulphate daily over Prolonged Periods in Simple Tertian Malaria. Vol. XI, p. 309. 1918.

VIII Oral Administration of Quinine Sulphate for Two Consecutive Days Weekly over Prolonged Periods in Simple Tertian Malaria. Vol. XI, p. 331. 1918.

IX A Comparison of the Results of Interrupted and Continuous Quinine Treatment. Vol. XI, p. 359. 1918.

X Oral Administration of Quinine Sulphate Grains 120 on Two Consecutive Days only in Simple Tertian. Vol. XI, p. 417. 1918.

XI Oral Administration of Quinine Sulphate Grains 90 on Two Consecutive Days Weekly over a Period of Three Weeks in Simple Tertian Malaria. Vol. XI, p. 421. 1918.

XII At what Time after Cessation of Quinine Treatment do Relapses occur in Simple Tertian Malaria ? Vol. XI, p. 425. 1918.

XIII Oral Administration of Quinine Sulphate Grains 90 on Two Consecutive Days only in Simple Tertian Malaria (Second Series). Vol. XII, p. 71. 1918.

XIV Quinine Bihydrochloride Grains 30 intramuscularly, and Quinine Hydrochloride Grains 30 orally, Daily for 12 days, in Simple Tertian Malaria Vol. XII, p. 197. 1918.

XV A Factor hitherto overlooked in the Estimation of the Curative Value of Treatments of Malaria. Vol. XII, p. 201. 1918.

XVI Intravenous Injections of Novarsenobillon in Simple Tertian Malaria. Vol. XII, p. 211. 1918.

XVII Oral Administration of Quinotoxin for two Consecutive Days only, in Simple Tertian Malaria. Vol. XII, p. 217. 1918.

XVIII. A Comparison of the Value of Continuous and Interrupted Quinine Administration in Simple Tertian Malaria (Second Communication). Vol. XII, p. 303. 1919.

XIX Intravenous Injections of Disodoluargol in Simple Tertian Malaria. Vol. XII, p. 339. 1919.

XX Intramuscular Injections of Collosol Manganese in Simple Tertian Malaria. Vol. XII, p. 345, 1919.

XXI Arsenic in Simple Tertian Malaria. Vol. XII, p. 371. 1919.

XXII Intramuscular Injections of Quinine Bihydrochloride Grains 15 on each of two Consecutive Days only, in Malignant Tertian Malaria. Vol. XIII, p. 63. 1919.

XXIII Oral Administration of Quinine Sulphate Grains 30 on each of two Consecutive Days weekly, over a Period of Five Weeks in Malignant Tertian Malaria. Vol. XIII, p. 69. 1919.

XXIV The Disappearance of Crescents under Quinine Treatment. Vol. XIII, p. 73. 1919

XXV Arsenic in Malignant Tertian Malaria. Vol. XIII, p. 75. 1919.

XXVI The Action of Arsenic and of Quinine on Quartan Malaria. Vol. XIII, p. 97. 1919.

XXVII Intravenous Injections of Novarsenobillon and Intramuscular Injections of Quinine Bihydrochloride in Simple Tertian Malaria. Vol. XIII, p. 101. 1919.

XXVIII Quitenine Hydrochloride in Simple Tertian Malaria. Vol. XIII, p. 117. 1919.

XXIX Oral Administration of Liquor Arsenicalis Minims 30 daily for 16 Days with Quinine Bihydrochloride Grains 15 Intramuscularly on the 1st and 2nd, 8th and 9th, 15th and 16th days, in Simple Tertian Malaria. Vol. XIII, p. 119. 1919.

XXX At what time after Cessation of Quinine Treatment do Relapses occur in Simple Tertian Malaria ? (Second Communication). Vol. XIII, p. 125. 1919.

XXXI The Time of Onset of the Paroxysms in Simple Tertian Malaria. Vol. XIV, p. 365. 1921.